

## REMARKS

### DETAILED ACTION AND RESPONSE

The Examiner states as follows:

Applicant's amendments and remarks, filed 12/5/03 and 3/11/04, are acknowledged. Amended claims 1-2, 6-7, 10-12, 16-18, 20-21, and 24 and new claims 35-46 are acknowledged.

Applicant's arguments, filed 12/5/03 and 3/11/04, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The interview summary provided by Applicants, filed 12/5/03, is accepted by the Examiner.

The information disclosure statement filed 7/7/03 (originally filed 4/17/03) fails to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP§ 609, because the PCT International Search Report is not a published document. It has been looked at by the Examiner but is not formally acknowledged as being considered on the merits.

Claims 1-24 and 35-46 are herein under examination.

Applicants acknowledge the above brief status recitation and thanks the Examiner.

#### *Claim Objections*

Claim 7 is objected to because of the following informality: There is a misplaced "d" on line 3 of claim 7. Appropriate correction is required. This objection is necessitated by amendment. Applicants traverse this objection and request reconsideration.

Applicants have amended the claim to remove the offending "d", and respectfully requests withdrawal of this objection.

#### *Claim Rejections - 35 USC § 112*

**Claims 20-24 and 45** stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by amendment. Applicants traverse this rejection and request reconsideration.

The Examiner states as follows:

Claim 20 recites the phrase "two different sites" which does not appear to

have support in the specification. Due to the introduction of this phrase without appropriate support in the specification, claims, or drawings as originally filed, this phrase is considered to be NEW MATTER. Claims 21-24 and 45 are also rejected due to their direct or indirect dependency from claim 20. This rejection is necessitated by amendment.

Applicants have amended independent claim 20 to remove the offending phrase "two different sites". Applicants, therefore, respectfully request removal of this section 112, 1<sup>st</sup> paragraph rejection.

Applicants note that the deletion of this phrase expands the scope of the claim, because the phrase dictated where the pair of tags will be placed, while without the phrase, the tags can be on the same amino acid residue within the polymerase. Thus, the amendment is not a narrowing amendment for it now covers a pair of tags irrespective of their sites of attachment.

#### ***Claims Rejected Under 35 U.S.C. § 112, Second Paragraph***

The rejection of claim 19 stands maintained and newly applied to new claims 18, 35-42, and 46 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants traverse this rejection and request reconsideration.

The Examiner states as follows:

Claim 19 (line 3) and new claim 42 (line 3) recite the phrase "mixtures or combinations thereof of the *Taq* polymerase" which is vague and indefinite. it is unclear what else may be included in these multiple entities besides *Taq* DNA polymerase I. Clarification of the metes and bounds of these claims via clearer claim wording is required. Applicants state this unclear phrase has been removed from claim 19, but it has not been removed. This rejection is maintained (claim 19) and necessitated by amendment (claim 42).

Claims 18, 35, and 36 are vague and indefinite due to the unclarity of citing an abbreviation, such as FRET; Correction is suggested by amending in of the full name in parentheses. Claims 37-42 and 46 are also rejected due to its dependency from claims 35 and 36. This rejection is necessitated by amendment.

Applicants have amended claims 18, 35 and 36 adding language to define the abbreviation FRET. Applicants have amended claims 19 and 42 to remove the phrase "and mixture or combinations thereof." Applicants, therefore, respectfully request withdrawal of these rejections.

Applicants note that the amendments to add what the abbreviation FRET stands for is not a narrowing amendment and not estoppel attaches.

### ***Claim Rejections - 35 USC § 102***

The rejection of **claims 1-5,7-9, and 20-23** is necessitated by amendment under 35 U.S.C. 102(a) and (b) as being anticipated by Williams (WO 00/36151 under 102(a)) and Brandis (Nucleic Acids Research, 1999, Vol. 27, No.8 under 102(b)). Applicants traverse this rejection and request reconsideration.

The Examiner states as follows:

This rejection is necessitated by amendment and reiterated for reasons of record. This rejection is made with the assumption that the phrase "two different sites" recited in instant claim 20 will be removed due to the presence of NEW MATTER...

Applicants state the tag on the polymerizing agent is not a substrate transiently held within the active site of the polymerizing agent during monomer incorporation, but is an atomic or molecular species that is part of the polymerizing agent. This is found unpersuasive as the claims fail to state that such a transient nature is excluded from the limitations. Therefore, the claims will be interpreted broadly and reasonably to include a transient nature of the composition. Applicants state there is no suggestion to covalent bonding a tag to the polymerizing agent itself. This is found unpersuasive as covalent bonding is discussed in the rejection below, and Applicants fail to present evidence that would render the rejection improper. Applicants state the present invention generates natural sequences instead of modified sequences. This is found unpersuasive as this potential aspect of their invention is not stated in the instant claims. Applicants make another assertion that the Williams/Brandis prior art do not disclose a polymerase having a covalently bound fluorescent tag that is directly involved in monitoring dNTP incorporation. This is found unpersuasive as the instant claims also fail to state that the tag is directly involved in monitoring dNTP incorporation. Claims 1-5, 7-9, and 20-23 as broadly and reasonably interpreted are anticipated by the Williams/Brandis prior art, as discussed below

As stated in the previous Office action, mailed 9/10/03, Applicants stated the critical difference between their invention and the prior art is that the tags in their invention remain associated with the polymerizing agent. This was found unpersuasive as the claims, as written, state a polymerizing agent and a tag without mention of whether this tag is transient or permanent. Applicants stated the Williams/Brandis prior art references did not disclose a tagged polymerizing agent. This is found unpersuasive as bonding inherently occurs between the polymerase and the tagged entity, as described, *infra*. Even though this bonding may occur transiently, it does occur which is encompassed in the broad reasonable interpretation of the tagged polymerase agent.

Williams discloses a *Taq* DNA polymerase (p. 8, lines 23-28) in which a fluorescently labeled dNTP (tag) is associated with the polymerase during monomer incorporation (p. 8, lines 1-9). Williams discloses a fluorophore and quencher pair being incorporated into oligo probes (p. 2, lines 16-18). The dNTP tag consists of a labeled nucleotide triphosphate (NTP) having a  $\gamma$ -phosphate with a fluorophore moiety attached and a quencher moiety that sufficiently prevents fluorescence until

incorporation of the NTP at which time the  $\gamma$ -phosphate with the fluorophore moiety is released and detected (p. 8, lines 10-20). As Webster's II New Riverside Dictionary defines a tag as a piece of something that identifies, classifies or labels; one reasonable interpretation of the quencher is a tag whose close presence to the fluorophore tag results in fluorescent signal disappearance (p. 2, lines 16-25). Williams discloses the fluorescence is detected when labeled dNTPs are incorporated into the strand and fluorescence is induced (p. 9, lines 28-29). Williams discloses that upon incorporation, the fluorescent dye molecule is released with pyrophosphate from the polymerase and then swept away from the parent DNA molecule by the flow (p. 10, lines 13-17), suggesting the polymerase's detectable property reverts back to its initial state. Williams discloses that as the polymerase moves along the DNA the nucleotide sequence is read from the order of released dyes (p. 14, lines 30-31). Williams discloses the possible presence of other polymerases, such as HIV reverse transcriptase, as stated in claims 5, 9, and 23. Williams discloses acquiring a sequence of images/movies (read outs) of fluorophores in order to track the path of single dyes involved in monomer incorporation (page 8, first paragraph; page 12, third paragraph; page 13, second paragraph; page 14, fourth paragraph) as well as data storage units that record detection (page 15, second and third paragraphs),

A 35U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is inherent (see MPEP 2131.01 (c)). Brandis discloses a *Taq* DNA polymerase I including an inherent characteristic that polymerases go through conformational changes (abstract). Brandis also discloses that a change occurs in a fluorescent label during the change in conformational states of the polymerase when nucleotide binding occurs as the polymerase is active (abstract). Voet et al. disclose a transition state theory allowing the understanding of how enzymes catalyze reactions (p. 332, col 2, first paragraph). Voet et al. disclose a high-energy (unstable) complex existing with covalent bonds during a bimolecular reaction (p. 332, col. 2, second paragraph)

Thus, Williams and Brandis anticipate claims 1-5, 7-9, and 20-23 of the instant invention.

Applicants are somewhat mystified by part of the Examiner's reasoning. The Examiner states:

Applicants state the tag on the polymerizing agent is not a substrate transiently held within the active site of the polymerizing agent during monomer incorporation, but is an atomic or molecular species that is part of the polymerizing agent. This is found unpersuasive as the claims fail to state that such a transient nature is excluded from the limitations.

Claim 1 states that "a fluorescence property of the tag undergoes a change before, during and/or after **each of a sequence of monomer incorporations.**" For the fluorescence property to undergo a change before, during and/or after each of a sequence of monomer incorporations, the tag on the polymerase must persist during each of the sequence of monomer additions. As stated in the

application, the duration of its persistence is not determined by the tag coming off or disassociating with the polymerase, but is due to a process called photo-bleaching where, eventually, the fluorophore stops absorbing or emitting light.

Even though, Applicants believe that the language of claims 1, 7, and 20 forces a conclusion that the tag on the polymerase must persist during the entire detected incorporation sequence (no read out would occur otherwise), Applicants have added a phrase to clearly state that the tag remains covalently bonded to the polymerase before, during and/or after each monomer incorporation in the sequence of monomer incorporations. Specific support, outside of the inherent support through the application, can be found at least at pages 17-22 (sequencing), 27-29 (data stream retrieval) and 32-36 (sequencing). These pages speak specifically to the interaction between the tag on the polymerase and the tag on the dNTP at each monomer incorporation (polymerase) or each monomer cleavage event (depolymerase, nuclease) to that a detectable property of either one or both of the tags is used to ascertain molecular incorporation or cleavage events.

Neither Williams nor Brandis discloses a polymerase or polymerizing agent having one or pairs of covalently bound fluorescent tags that are capable of directly monitoring a sequence of monomer (dNTP) incorporation events, Williams/Brandis cannot, therefore, anticipate the invention claimed in claims 1-5, 7-9 and 20-23. Furthermore, neither Williams nor Brandis render the present inventions obvious because Williams/Brandis do not disclose, teach or suggest covalently bonding one or pairs of tags to the polymerizing agent. In fact, taking one of the tags in the Williams process and tying it to the polymerase would render the Williams/Brandis process wholly inoperable because the tags on the dNTPs would always be active and only inactive during monomer incorporation. However, the other dNTP signals would significantly interfere with detection of dark periods for a signal fluorescing monomer. Applicants, therefore, respectfully request withdrawal of this section 102 rejection.

### ***Conclusion***

The Examiner states as follows:

Claims 6, 10-17, and 43 stand allowable.

Claim 44 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant now believe that claims 10-19 and 44 are allowed or allowable, claims 35-42 and 46 are allowable, and claims 47 and 43 are allowable, where claim 47 is rewritten claim 6 in

independent form.

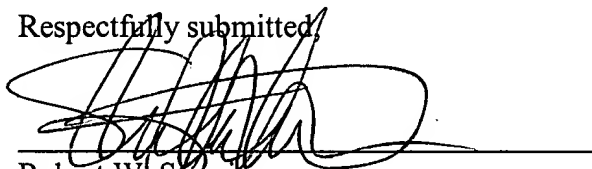
Applicants also believe that the amendments to claims 1, 7 and 20 make the claims allowable due to the Applicants' reinforcing the fact that the tag or tags on the polymerizing agent remain covalently bonded to the polymerizing agent during a sequence of incorporation events to produce a read out of the events.

Applicants, therefore, respectfully request that the amended claims be passed onto allowance.

If it would be of assistance in resolving any issues in this application, the Examiner is kindly invited to contact applicant's attorney Robert W. Strozier at 713.977.7000

Date: **June 18, 2004**

Respectfully submitted,



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